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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/622,011	SABA, JULIE D.	
	Examiner	Art Unit	
	IQBAL H. CHOWDHURY	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-14,16,20-22,26,27 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14, 16, 20-22, 26-27 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 12-14, 16, 20-22, 26-27 and 30 are currently pending in the instant application.

In response to a previous Office action, a non-final action (mailed on September 18, 2008), Applicants filed a response on February 18, 2009 is acknowledged.

Claims 12-14, 16, 20-22, 26-27 and 30 are under consideration.

Applicants' arguments filed on February 18, 2009 have been fully considered but they are found unpersuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Maintained- Claims Rejections- 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 12-14, 16, 20-22, 26-27 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lanterman et al. (Biochem J. 1998 Jun 1; 332 (Pt 2): 525-31), Kim et al. (Genetics. 2000 Dec; 156(4): 1519-29) and in view of Melendez et al. (Gene. 2000 Jun 13; 251(1): 19-26 and GenBank Accession No. AF266756, created 6/1/2000). This rejection has been discussed at length in the previous office action mailed on 8/18/2008 and the rejection is maintained as discussed in the previous office action and for the following reasons.

Instant claims are drawn to a method of identifying an agent that modulates sphingolipid metabolism by culturing a mutant yeast strain comprising a null allele of a gene encoding a dihydrosphingosine-1-phosphate lyase 1 (DPL1) or a gene encoding a long chain base kinase 4(LCB4) or a gene encoding yeast sphingosine resistance 2 (YSR2) protein and expressing a gene encoding a non-endogenous sphingolipid pathway component of a sphingosine kinase of SEQ ID NO: 21.

Lanterman et al. teach creation of a mutant yeast strain, which comprises a null allele of DPL1 (dihydrosphingosine phosphate lyase) gene and an active LCB4 (sphingosine kinase of yeast), and a method of identifying an agent which modulates sphingosine kinase (LCB4) using yeast strain by measuring the production of sphingosine-1-P, which reflects the activity of sphingosine kinase (SK). Lanterman et al. also teach an assay method using said mutant yeast for screening an inhibitor of yeast SK (LCB4) and tested known mammalian SK inhibitor (D,L)-threo- dihydrosphingosine against said yeast SK in said mutant yeast cell to see whether the kinase is inhibited or

not in presence or absence of the candidate agent (D,L)-threo- dihydrosphingosine. Lanterman et al. also teach the creation of double mutants of ΔDPL and ΔLCB4 (equivalent of SK), i.e. Lanterman et al. teach a mutant yeast strain having double mutations such as ΔDPL and ΔLCB4 (equivalent of SK), which can be used for expressing heterologous SK in particular human SK for screening inhibitors of said human SK for therapeutic intervention against human diseases caused by deregulation of sphingolipid pathway. It would have been obvious to one of ordinary skill in the art to use this system to identify an agent, which would inhibit sphingosine kinase, which produces S-1-P as Lanterman et al. clearly show that the ΔDPL1 are growth inhibited only in the presence of an active sphingosine kinase. Lanterman et al. do not teach transforming said mutant strain with non-endogenous human SPHK1 gene encoding human sphingosine kinase 1, which is complimentary to LCB4 of yeast sphingosine kinase, which is inactivated in the mutant yeast strain and expressing said SPHK1 gene.

Kim et al. disclose a method of analyzing sphingolipid metabolism in a mutant S. cerevisiae having disruption mutants of DPL1 (lyase), or LCB4 (kinase), or YSR2 (phosphatase) or in combination and assay methods of sphingolipid metabolism. Kim et al. also disclose that when DPL1 and YSR2 genes are mutated in yeast strains, it results in the enhancement of sphingosine-1-phosphate (S-1-P) level either in the culture medium or inside the cell to growth inhibitory levels but that ΔDPL1-LCB4-YSR2 triple mutant does not accumulate toxic levels of S-1-P. Kim et al. further teach that over expression of LCB4 i.e. kinase in triple mutant yeast strain ΔDPL1-LCB4-YSR2

results in the 500 fold accumulation of S-1-P than control, which is also extremely growth inhibitory to the mutant cells comprising triple mutant ΔDPL1-LCB4-YSR2 yeast strain, but over-expression of LCB4 in wild type yeast strain do not have such effects. As such Kim et al. clearly show that the triple mutant strains growth inhibited only in the presence of an active heterologous sphingosine kinase gene. Kim et al. do not teach any agents by using mutant yeast system and transforming said mutant strain with non-endogenous human SPHK1 gene encoding human sphingosine kinase 1 and expression.

Melendez et al. teach a human sphingosine kinase (SPHK1), molecular cloning, and expression in host cells, functional characterization and tissue distribution. Melendez et al. also teach that sphingosine-1-phosphate (SPP), the product of sphingosine kinase, is an important signaling molecule with intra- and extracellular functions. Melendez et al. further teach an assay method to identify an inhibitor such as D,L-threo-dihydrosphingosine or N,N-dimethyl-sphingosine, which inhibit the human SPHK1 kinase and subsequently alter the sphingolipid metabolism.

Lanterman et al. and Kim et al. provide the motivation at the time of the invention was made to use a mutant yeast strain, wherein sphingolipid metabolic pathway is well characterized by disrupting endogenous genes important for sphingolipid metabolism and an assay method of LCB4 kinase (a sphingosine kinase) by which an activator or inhibitor of SK can be evaluated in terms of S-1-P formation. Lanterman et al. and Kim et al. also provide motivation of using yeast strain null of DPL1 or LCB4 or YSR2 or double or triple mutant strain, made this strain attractive for using as a tool to one of

ordinary skill in the art for testing human gene such as sphingosine kinase, which is an important component of sphingolipid metabolism to identify an inhibitor for treating human against sphingolipid metabolic disorders such as cancer. However, Melendez et al. provide the motivation of using a human SK and an assay method to identify an inhibitor such as D,L-threo-dihydrosphingosine or N,N-dimethyl-sphingosine, which inhibit the human SPHK1 kinase and subsequently alter the sphingolipid metabolism in African green monkey cell Cos7 cell.

Thus, It would have been obvious to one of ordinary skill in the art at the time of the invention was made to combine the teachings of Lanterman et al., Kim et al. and GenBank Accession No. and Menendez et al. for developing a method of assay for inhibitors of sphingosine kinase (SK) to identify an agent as taught by Lanterman et al. and Kim et al. by using mutant ΔDPL1 and ΔLCB4 or a ΔDPL1, ΔYSR2, ΔLCB4 yeast strain of Kim et al. and transformed with human SPHK1 gene of GenBank Accession No, which modulates sphingolipid metabolism by monitoring either 1) the growth of mutant ΔDPL1, ΔLCB4 or ΔDPL1, ΔYSR2, ΔLCB4 yeast strain, as Lanterman et al. and Kim et al. each shows that these strains are growth inhibited in the presence of an active sphingosine kinase such as SK, or 2) the concentration of S-1-P, which would decrease if the agents were active to arrive the claimed invention. It would have been also obvious to one of ordinary skill in the art to identify an agent which alters the growth of mutant yeast strain or accumulation S-1-P concentration to identify an agent would be expected to prevent human diseases like cancer and muscular disorders in which S-

1-P enhances cell proliferation, calcium mobilization or Raf/MEK/ERK signaling pathway or decreases apoptosis.

One of ordinary skill in the art would have been further motivated to use human sphingosine kinase 1 (SPHK1) gene instead of yeast sphingosine kinase gene in order to obtain an agent or modulator of the human sphingosine kinase to use that agent as a therapeutic measure against human diseases like cancer and muscular disorders.

One of ordinary skill in the art would have a reasonable expectation of success because use of non-endogenous human gene in a mutant yeast strain, where the sphingolipid metabolism is well characterized having disrupted endogenous genes, is customary and widely used in the art for functional studies of said non-endogenous human gene as well as identification of modulators of said human gene for therapeutic intervention.

Arguments:

Applicants' argue that "While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in a nonobviousness inquiry, the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." In the present case, Applicant submits that the PTO provides no reason that would have prompted a person having ordinary skill in the art to select, as a starting point from among myriad possible cell types that were available when the present application was filed, the mutant yeast

strains of Kim *et al.* as a "lead compound", and then to modify them to express human SK in order to screen for SK inhibitors.

Applicants also argue that no motivation or reason exists in the prior art for the person having ordinary skill to select the mutant yeast strains taught by Kim *et al.* over other available options known at that time, such as using the cell lysates described in Melendez *et al.* Applicant submits that if anything, the skilled person would have been more likely to use the cell lysate- based assay described by Melendez *et al.* because the Melendez assay would have required no modification in order to be used as a screen for SK inhibitors; the Melendez assay would also have had the added advantage of employing mammalian cell lysates. The skilled person would have selected the Melendez assay with an expectation of success because that assay was fully described by Melendez *et al.* and was already functional without requiring modification.

Furthermore, Applicant's argue that Lanterman *et al.* provide good reason to steer the skilled person from selecting the mutant yeast cells of Kim *et al.* in favor of the assay described by Melendez *et al.,* where Lanterman *et al.* disclose that *(D,L)-threo-dihydrosphingosine,* a known inhibitor of mammalian SK, failed to inhibit the yeast SK enzyme (see abstract, page 527, last paragraph and Figure3), suggesting that molecular pathway components of the yeast sphingolipid metabolism system may have structural and functional differences from the mammalian sphingolipid metabolism system. On the contrary, in view of Lanterman *et al.* the person having ordinary skill in the art would if anything has believed that human SK would be incompatible with the yeast sphingolipid metabolism pathway.

Response:

Applicant's amendments to the claims and arguments have been fully considered but they are found unpersuasive. The Examiner acknowledges the KSR ruling but applicants statement is not correct, i.e. the correct statement would be "While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in a obviousness inquiry (not nonobviousness inquiry), the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." This indicates that before this KSR ruling, obviousness test was very rigid for Examiner to establish a prima facie case based on 1) teaching, 2) suggestion, and 3) motivation and without a valid motivation the obviousness rejection was not prima facie to combine the prior arts to arrive the claimed invention but now the rigid application of TSM is rejected by the Court, i.e. this ruling made the Examiner to use TSM Test non-rigid or flexible way with reasoning, and it is reasonable to combine the teachings of the prior art to arrive the claimed invention.

Regarding choosing the mutant yeast cell as a starting material of Kim et al. or Lanterman et al. one of ordinary skill in the art would obviously chose the mutant yeast cell of Kim et al. as a starting material because the sphingolipid metabolism is well characterized in that mutant yeast cell by disrupting endogenous genes important for sphingolipid metabolism and furthermore, Kim et al. clearly shows that accumulated S-1-P inhibits cell growth of said mutant S. cerevisiae, which is the important limitation of the claimed invention as a readout system that would cost much less than enzyme

assay as taught by Melendez et al. which requires expensive substrates (even radioactive materials), necessary reagents and expensive instruments for readout such as scintillation counter or spectrophotometer.

Contrary to applicants arguments Kim et al. and Lanterman et al. indeed teach assay method of sphingosine kinase (SK) by which an activator or inhibitor of SK can be screened by determining S-1-P formation. Lanterman et al. and Kim et al. also teach yeast strain null of DPL1 or LCB4 or YSR2 or double or triple mutant strain, although do not teach using a human SK. However, Melendez et al. teach a human SK and an assay method to identify an inhibitor such as D,L-threo-dihydrosphingosine or N,N-dimethyl-sphingosine, which inhibit the human SPHK1 kinase and subsequently alter the sphingolipid metabolism.

Regarding the argument that mammalian SK inhibitor (D,L)-threo-dihydrosphingosine, does not inhibit yeast SK and further suggestion that yeast sphingolipid metabolism system may have structural and functional differences from the mammalian sphingolipid metabolism system and human SK would be incompatible in yeast cell. This is not found persuasive because enzyme function depends on structure, catalytic and substrate binding domain of the enzyme but not on the cellular factor of sphingolipid metabolism system, wherein a modulator may compete with substrate or binds active site thereby modulating enzyme activity. Protein sequence database search against human SK of SEQ ID NO: 21 revealed that a yeast protein, which has highest homology to SEQ ID NO: 21, is only 18% homologous, indicating the structurally diverse nature of the yeast SK related protein. In addition, cellular factor of

the metabolic system is not relevant here because cellular factor of the metabolic system only affects promoter activity of the expressed enzyme not the enzyme activity. Furthermore, claimed invention is not for identifying yeast SK inhibitor but rather a heterologous human SK and one of skilled artisan would be motivated to use mutant yeast cell of Kim et al. by knowing that yeast SK is resistant to human SK inhibitor. Thus, selecting yeast cell for expressing human would be advantageous for screening human SK inhibitor in view of yeast SK resistant to human SK inhibitor. Besides, human and yeast cells are eukaryotic cell, where cellular components and metabolic pathways are very similar in both human and yeast cell than prokaryotic cell. Therefore, human SK will have similar function or activity in yeast cell like human cell. In addition, claims are not required to any inhibitor or use of yeast SK, but rather an assay of human SK activity by which a modulator can be identified in a well known yeast model system, which is taught by Lanterman et al., Kim et al. and Melendez et al. Therefore, applicant's conclusion is incorrect. Therefore, the rejection is maintained.

Conclusion

No claim is in condition for allowance.

Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution. **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed, can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Iqbal Chowdhury, Patent Examiner
Art Unit 1652

/Nashaat T. Nashed/

Supervisory Patent Examiner, Art Unit 1652